



**[Billing Code 4140-01-P]**

**DEPARTMENT OF HEALTH AND HUMAN SERVICES**

**National Institutes of Health**

**Request for Information: Main Study Design for the National Children's Study**

AGENCY: National Institutes of Health, HHS.

ACTION: Notice.

**SUMMARY:** The Eunice Kennedy Shriver National Institute for Child Health and Human Development (NICHD), National Institutes of Health (NIH), is issuing a Request for Information (RFI) as part of the National Children's Study's (NCS) effort to engage communities and receive public input on specific design questions for incorporation into the Main Study Design of the NCS. The information obtained from RFI responses will be used to guide the construction of decision points or parameters for the Main Study design over the next 12-18 months. This RFI was preceded by a workshop with the National Academy of Sciences which posed similar questions. For background information on this workshop, please visit:

<http://www.nationalchildrensstudy.gov/research/workshops/Pages/nationalacademyofsciencesworkshop.aspx>

**DATES:** RFI Release Date is February 11, 2013. Response Close Date is February 25, 2013.

**ADDRESSES:** To respond by February 25, 2013, please submit comments via email to [NCS\\_RFI@mail.nih.gov](mailto:NCS_RFI@mail.nih.gov). Please include citations for any references or reports that can be used as source material.

**FOR FURTHER INFORMATION CONTACT:** Questions about this request for information may be directed to Kate Winseck, MSW, The National Children's Study, Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, 6100 Executive Blvd., Rm. 5C01, Bethesda, MD 20891, [NCS\\_RFI@mail.nih.gov](mailto:NCS_RFI@mail.nih.gov), 301-594-9147.

**SUPPLEMENTARY INFORMATION:** The National Children's Study is a congressionally mandated longitudinal birth cohort study intended to examine the effects of environmental exposures on the growth, development, and well-being of children. The NCS was mandated by the Children's Health Act of 2000 (Public Law 106-310). The Study consists of several components, including: a pilot or Vanguard Study, a Main Study focused on exposure-response relationships, substudies embedded in the Vanguard Study or the Main Study, and formative research projects. Data collection for the Vanguard Study began in January 2009. The design was changed in 2010 from a door-to-door household recruitment model to include an Alternate Recruitment Study

(ARS). The ARS tested three different recruitment strategies that differed as to initial

point of contact with potential participants - direct outreach, household-based through an NCS contractor, and provider-based through a licensed health care practitioner.

Currently the NCS is testing, through Provider-Based Sampling Substudy, a further refinement of the provider-based sampling and recruitment using hospitals and birthing centers in addition to clinics and health care provider offices that are sampled.

Between the summer of 2011 and the fall of 2012, the NCS held a series of meetings with federal and non-federal statistical sampling experts and others to discuss the most effective sampling approach and design for the Main Study. The NCS had multiple separate discussions and consultations with additional individuals and organizations. Based on these extensive discussions and consultations, the NCS is proposing the use of a multi-stage probability sample for the Main Study. The NCS plans to enroll women through multiple entry points into the Main Study, such as perinatally at hospitals and birthing centers, and prenatally through prenatal care providers.

Additionally, women whose children are already enrolled will be followed as a preconception sample of subsequent births. Lastly, about 10% of the total number of participants to be recruited would be set aside for recruitment of a convenience sample for populations with characteristics or exposures of particular scientific interest that would likely be underrepresented in the other strata.

The questions solicited in this RFI focus on how much the NCS should emphasize prenatal data collection, and what the NCS could anticipate gaining through the prospective data collection compared to retroactive data acquisition and the use of extant sources such as medical records, other databases and modeling. The issue is not whether

to have a prenatal stratum, but what proportion of NCS resources should be devoted to the effort.

Responses to this RFI will be used to inform the Main Study design.

## **Proposed Main Study Design**

### **1. Goals and Outcomes**

The primary objective of the NCS is to examine relationships among exposures and outcomes that affect children's health and development. These factors include environmental exposures (with a broad definition of environment) and biological/genetic context. The NCS is not a study in a conventional sense. It will primarily function as a high quality data collection platform for researchers to explore hypotheses, access biospecimens and environmental samples, and analyze data. The Study's objectives stated in the Children's Health Act of 2000 are presented, along with the respective design considerations, in Table 1.

**Table 1:** The Main Study objectives as stated in the Children's Health Act of 2000 with design implications.

<b>Study Objectives</b>	<b>Sample and Study Design Implications</b>
Evaluate the effects of both chronic and intermittent exposures on child health and human development	Visit schedule with an emphasis on documenting early exposures and events High retention of children is important to gather
Investigate basic mechanisms of developmental disorders and environmental factors	Broad scope of data collection to determine the association and influence of exposures on outcomes supplemented and informed by formative research program
Perform complete assessments of environmental influences on children's well-being	Broad scope of exposure and outcome data collection supplemented by personal health records
Gather data from diverse populations of children including prenatal exposures	Need to recruit diverse population groups and capture prenatal exposures

Consider health disparities among children	Ensure sampling of disadvantaged population groups (in terms of exposures, education, socioeconomic status, etc.)
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## **Exposures and Outcomes**

A non-exhaustive list of examples of exposures of potential interest includes:

- Natural products and industrial chemicals and byproducts in the air, water, soil, and commercial products;
- Pharmaceuticals used for therapy and in the environment;
- Ionizing and non-ionizing radiation
- Proximity to manufacturing, transportation, and processing facilities
- Living with animals, insects, plants, media and electronic device exposure,
- Noise
- Access to routine and specialty health care
- Structured and unstructured learning opportunities
- Diet and exercise
- Family and social network dynamics in a cultural and geographic context

A non-exhaustive list of examples of outcomes of potential interest includes:

- Premature birth
- Birth defects
- Growth and development
- Interpersonal relationships and bonding
- Inflammatory processes including allergies, asthma, and infections
- Epigenetic status

- Epilepsy and other neurologic disorders
- Cardiovascular function
- Cancer
- Multidisciplinary, multidimensional aspects of sensory input
- Autism and other neurodevelopmental disorders
- Learning and behavior
- Precursors and early signs of chronic diseases such as obesity, asthma, hypertension, and diabetes

Both public health impact (based on severity, as well as prevalence) on the overall population of children and scientific opportunity will inform the prioritization of mechanisms to be investigated. Examples of conditions of potential interest are shown in Table 2.

**Table 2:** The prevalence estimates per 100,000 for selected childhood illnesses\*

Condition	Estimated Prevalence per 100,000
Obese	17,000
Overweight	30,000
Premature Birth	12,500
Learning Disorders	5,000
Asthma	5,000
Birth Defects (aggregate)	3,000
Autism Spectrum Disorders	1,000-3,000
Schizophrenia	1,100
Congenital Heart Disease	800
Epilepsy	470
Childhood Cancers	320
Down Syndrome	125
Fragile X Syndrome	50

\*Note that the legal federal threshold for a rare disease is a prevalence of about 64 per 100,000.

The prevalence of many of the conditions in Table 2 is possibly underestimated due to disparities in health and access to health care, limiting diagnosis. In addition, the prevalence presented represents only the level of each disease spectrum where formal evaluation and intervention are required. Children with less severe symptoms or with restricted access to health care may have health impacts from these conditions but not rise to a level captured by formal health care records.

### **Use of Exemplar or Illustrative Hypotheses**

Because there is no universal and unambiguous definition of health, the NCS plans to employ investigation of a select number of exposure outcome illustrative hypotheses. Illustrative hypotheses will be prioritized with consideration for the public health importance of the outcome, availability of study visit measurement assessments, and sampling considerations such as sample matrix, specificity and stability of analytes, informative value, and options for other study visit measurement assessments to collect the same kind of information. Each exposure will be assigned to each outcome in a matrix table to generate illustrative hypotheses as a reference point to test many other hypotheses, including those that may not be envisioned at this time. For example, the appearance of a chronic inflammatory condition may result from an interaction between host characteristics that include genotype and exposures that may include diet, microbiome, and infection. Another example may be that exposure to nuts may have a beneficial effect in some people and may provoke a life threatening allergic response in others.

In this illustrative hypothesis paradigm, select exposures proposed as surrogates for additional exposures are:  
analysis of

- Heavy metals
- Pesticide residues
- Semi-volatile organic compounds, and
- High frequency sound

in samples of

- Household dust
- Blood
- Urine, and
- Questionnaires on exposures including social environment.

The select outcomes proposed as surrogates for additional outcomes are:

- Linear growth rate and body mass index as a surrogate for general health
- Metabolic screen of serum total protein, blood urea nitrogen, cholesterol, iron, and calcium for nutrition and dietary assessment
- Frequency and duration of health system encounters for respiratory illness for pulmonary health, and
- Timing of standard neurodevelopmental landmarks and any deviation from adjusted trajectory for cognitive and social development.

Future research questions for the NCS are likely to be complex and involve multiple “exposures” from behavioral, environmental, and sociologic domains along with phenotypic information in relation to an outcome. The hypotheses that will be pertinent to the field 15 to 20 years from now are impossible to predict and therefore model. We propose this matrix as an exemplar, and will focus our Study design on the construction of a robust platform of data from a national probability sample.



## **2. Proposed Study Design**

### **Target Population**

A birth cohort of children born to mothers residing in the United States will be the primary target population. In addition, populations that might otherwise be underrepresented in the cohort on the basis of exposures, demographics, or other factors will be supplemented through targeted recruitment.

### **Study Sample Size**

The proposed sample size will be about 100,000 live births.

### **Sampling and Recruitment Strategy**

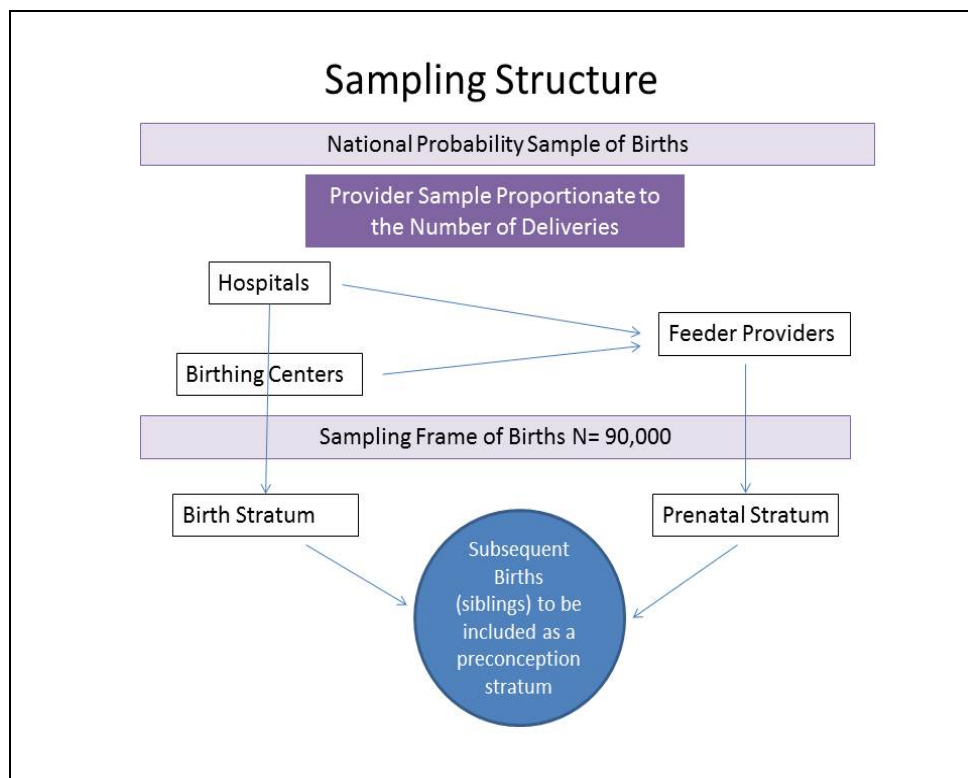
The NCS is proposing a multi-stage probability design for the Main Study. The rationale for using the proposed approach is the perception of differences among the characteristics of each recruited population that have analytic, logistical, or cost implications and the difficulty of identifying and enrolling a single generalizable sample of women, spanning from preconception to birth, in a practical manner. The design will be based on a national probability sample recruited through health care providers as the major component of the overall Study sample, with about a 10 percent of the total sample size set aside for targeted populations for addressing additional questions of scientific interest. A health care provider can be a hospital, birthing center, community based practitioner, or clinic.

The target population is children born to mothers in the United States during a predefined recruitment period. In order to sample this population we propose taking a probability sample (with probability proportionate to the number of deliveries) from a national listing of hospitals and birthing centers. From these sampled hospitals and

birthing centers a second stage of the sampling design will be a listing of prenatal care providers that “feed” patients for delivery at the hospital. From these “feeder” providers, we will attempt to recruit women during their prenatal period. These women would be considered a prenatal stratum of the design (Figure 1).

Some women may not be enrolled prenatally. This may be because they did not seek prenatal care, or because they sought care from a provider not selected by the steps above. These women could be enrolled at the hospital at delivery, and would be considered a part of the birth stratum of the design.

**Figure 1.** The strata of the Main Study probability sample, a national sample of births, with recruitment into birth, prenatal or preconception strata.



The most cost effective and simplest approach is to enroll women perinatally. About 98 percent of pregnant women in the United States deliver at hospitals or birthing

centers, so the recruitment opportunity is greatest at birth. The proportion of the entire sample that can be enrolled prenatally and perinatally can be adjusted by the number of prenatal providers engaged, the number and duration of opportunities the design uses to enroll participants, and the logistics and efficiency of each location.

NCS field experience to date is mixed with regard to the cost, ease, accuracy, and cooperation of engaging community providers. One consideration is that women seek prenatal care at various times along the continuum of pregnancy with factors such as access, affordability, complex medical conditions, etc. influencing the composition and bias of any prenatal sample of women.

Regardless of the point of entry into the Study, women enrolled in the Study would be followed and any subsequent births of siblings could also be enrolled in the Study. These subsequent births, or higher birth order siblings, would be considered a preconception stratum of the design as there would be environmental assessments prior to the conception of the sibling as a result of already being enrolled in the Study.

What is important to note is that women recruited from health care providers will have different timing for their entry into the Study, and therefore, different amounts of information collected. Women recruited prenatally from their prenatal care provider will have the opportunity for prospective environmental assessments during the prenatal period. Women recruited through hospitals will have data collected at the birth visit that may be representative of a portion of the prenatal period (such as the collection of a vacuum cleaner bag of dust and questionnaire data), however this would be collected retrospectively and the inference period of the samples will vary. Study visits and assessments from the birth visit onward will be uniform across strata (Table 3).

**Table 3.** Summary of the data collection opportunities from the strata in the Main Study probability sample. The x's are a representation of the quantitative measure of the amount of information that can be gathered from the stratum at a particular point in the pre- or perinatal period, with xxx referring to the greatest amount of information.

Point of Entry Into Study	Opportunities to Obtain Prospective Biological Specimens and Environmental Samples					
		Birth	3 <sup>rd</sup> Trimester	2 <sup>nd</sup> Trimester	1 <sup>st</sup> Trimester	Preconception
	Birth	xxx	-	-	-	-
	Prenatal	xxx	xxx	xx	x	-
	Sibling	xxx	xxx	xxx	xxx	xxx

The supplemental, or targeted studies, could be outside the cooperating institutions and would target populations that are underrepresented for any reason of scientific interest. An example of one of these cohorts would be a small sample of pregnant women residing in a community where pressure extraction for natural gas by hydraulic fracturing, or fracking, is taking place, and thus, the scientific interest lies in the environmental exposure. However, the area or number of births may be so small that the probability of selection into larger probability samples is low. These cohorts could be part of ancillary studies that would leverage the resources of the NCS. These targeted cohorts are not expected to be part of the larger probability samples described above, although probability-based approaches may be used. These cohorts are intended to be analyzed independently. We propose a scientific review process to screen proposals for targeted cohorts for alignment with the Study goals and prioritization with available resources.

#### **a. Retention Strategy**

The primary recruitment mechanism will be through health care providers, with the

birth stratum recruited through hospitals and birthing centers, and the pregnancy stratum recruited through prenatal care providers who feed into the hospitals and birthing centers participating in the birth sample.

A key goal for the NCS Main Study is to obtain information on the health and developmental outcomes of participants as they move through childhood, adolescence, and early adulthood. To answer many of the potential scientific questions, it will be essential to retain a sample of sufficient size throughout the course of the Main Study to obtain robust longitudinal data. Determining expected rates of retention of participants through pregnancy to birth and beyond is a key part of the analytic plan for the Vanguard (Pilot) Study. Retention of participants from visit to visit will be carefully monitored.

Specifically, the NCS will use the following data from the Vanguard Study to monitor and plan retention strategies for the Main Study:

- The proportion of consented women who participate in at least one data collection Study visit
- The proportion of women enrolled during pregnancy and participating in all data collection visits through the birth of a child who is enrolled into the Study
- The proportion of women who receive a pre-birth data collection visit who also receive a successful birth visit, and
- The proportion of women enrolled during pregnancy and participating in all data collection visits of an enrolled child.

Retention challenges and solutions will likely vary by the nature of the visit, the length of time between visits, and the participant's stage in the Study cycle. Information collected from field data collectors represents a critical source of data from which to

evaluate the feasibility and acceptability of the NCS Vanguard Study. Our ability to utilize these data to inform subsequent decisions requires coordination of several operational efforts, including hiring, training, and monitoring of field staff and the development of instruments, Study procedures, and case management documentation. For example, unit nonresponse – both initial and due to attrition – will be assessed systematically through the administration of a Nonrespondent Questionnaire. Additionally, our understanding of participant reactions to introducing the collection of biospecimens from infants will be informed by these multiple sources.

#### **b. Study Visit Schedule**

Both the Vanguard Study and the Main Study emphasize data collection early in pregnancy and early in child development because the largest knowledge gaps, and perhaps the most critical events, occur during those time periods. Consequently, pregnancy data collections for are scheduled twice, if possible, prior to approximately 20 weeks gestation and once later in pregnancy. Data collections for children are scheduled at birth and every 3 months for the first year and every 6 months until 5 years old, for a total of 13 opportunities for data collection. Seven of the opportunities will be face-to-face encounters and may include biospecimen and environmental sample collection (<http://www.nationalchildrensstudy.gov/research/workshops/Pages/NCS-proposed-example-outcome-exposure-table.pdf>). The other six are remote data collections, typically by telephone interview. Subsequent data collections have not been scheduled, but will be on average about every other year until 21 years old, for a total of 8 additional data collection opportunities. In sum, 21 data collection opportunities per child are planned, but that may change based upon experience from the Vanguard

phase, scientific opportunity, logistical factors, and resources available. Scheduling the majority of data collection within the first five years of life will address both the critical knowledge gaps, as well as maximize data collection while retention of participants is highest.

### **c. Study Visit Structure**

Multiple modalities for data collection are under evaluation, with the current plan based on a core questionnaire model administered at every childhood visit plus supplemental modules to be administered to specific participants or subpopulations based on events and conditions such as age, developmental stage, and other triggers such as specific exposures or hospitalizations. While the core questionnaire is intended for all participants, supplemental modules may be administered on a missing by design basis, to leverage the large Study population and extend resources. In addition, the visit schedule is flexible, in that children will not have assessments administered precisely at a given age, but instead, within a window of several weeks around a particular age to improve compliance and to capture data across a range of specific ages. The module-based visit strategy should provide an opportunity to collect information about very specific exposures or outcomes while decreasing burden on respondents as all the modules will not be offered to all participants.

### **Information Requested**

This RFI invites the scientific community, health professionals, and the general public to provide comments and suggestions on the following topics:

1. What should be the criteria for the stratum allocation decision between perinatal and prenatal enrollment and what evidence is available to support an assessment of each criterion? Examples include:
  - a. Recruitment costs, which include the costs of constructing the frame and the relative costs and efficiency of enrolling a participant;
  - b. Generalizability. What population is being represented?
  - c. Extent of exposures and other information that can be gathered. By definition, women who enter the study at the birth visit will have more limited data on prenatal exposures than participants enrolled during the prenatal period; while prenatal participants will have less information on prenatal exposures (and much less information on preconception exposures) than the subsequent births to already enrolled mothers or a separate preconception sample.
2. What should be the allocation of sample cases among the various strata? Assume that 10% of the sample is reserved for preconception and special studies; then, the allocation involves the remaining 90,000.
  - a. One option is the current proposal which is about a 50-50 split or 45,000 participants in each.
  - b. Another option is something like an 80-20 split allocated between birth and pregnancy, with the pregnancy sample used to form the basis for imputing prenatal exposures (after using medical records for the mothers to get as much prenatal information as possible).



- c. Yet another option is like an 80-20 split allocated between pregnancy and birth, with the birth sample used to form the basis for providing generalizability to the data analysis.
  - d. One extreme could be the entire initial enrollment allocated to the birth stratum, with studies of prenatal and preconception exposures using primarily the subsequent births to originally enrolled mothers.
  - e. At the other extreme, most of the sample could be allocated to the prenatal stratum with a small birth sample consisting of women who did not receive any prenatal care and are enrolled at the hospital.
3. Given the challenge as stated in the Children's Health Act of 2000 to "perform complete assessments of environmental influences on children's well-being," does the proposed visit schedule and environmental sample collection (<http://www.nationalchildrensstudy.gov/research/workshops/Pages/potential-environmental-exposures-of-interest.pdf>) balance the complex requirements? Specifically comment on the proportion of different types of data collection—primary environmental sample collection, use of biological specimens for biomarkers of exposure, and use of secondary sources including retrospective analysis for environmental exposures. Considerations may include:
- a. Are the proposed measures (biomarkers, questionnaires, physical measures) the most appropriate to assess exposures of interest? If not, what measures should be taken?
  - b. On what decision points should the NCS prioritize exposure assessments? Some examples of factors to consider are:

1. Potential public health impact of the outcome
2. Technical feasibility including timing of data collection with regard to potential developmental vulnerability
3. Scientific opportunity to address knowledge gaps and illuminate developmental pathways

This RFI is for planning purposes only and should not be construed as a solicitation for applications or proposals and/or as an obligation in any way on the part of the United States Federal government. The Federal government will not pay for the preparation of any information submitted, and/or for the government's use of that information. Additionally, the government cannot guarantee the confidentiality of the information provided.

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